

In this study, we have actually used calcidiol, which increased serum 25 OH vitamin D levels from 10 to 30 ng/ml and those of calcitriol from 84 to 100 pmol/L. In addition 1.2 g/day of elemental calcium was given as CaCO₃ for phosphate binding. C-terminal parathyroid hormone levels stabilized for 18 months in spite of a glomerular filtration rate decline from 25 to 15 ml/min, suggesting a decrease in parathyroid hormone secretion. Hyperparathyroidism suppression was furthermore evidenced by a decrease of alkaline phosphatase and bone remodeling parameters.

Meanwhile, two cohort studies of 40 young adults with childhood-onset end-stage renal disease have been reported, which documented a coronary calcification prevalence of 92% in Heidelberg and 10% in Berlin, although biographical and therapeutical characteristics were comparable at the exception of vitamin D therapy that was based in Heidelberg mainly on 1 α OH vitamin D (eightfolds greater yearly dose), whereas in Berlin, it was based on 5750 IU/day of vitamin D₃, a dose which according to Garabedian yielded approximately 60 ng/ml of serum calcidiol.³

Therefore, we would like to propose that in predialysis as in dialysis patients, activated vitamin D be evaluated against placebo provided plain or 25 OH vitamin D₃ has first stabilized their 25 OH vitamin D serum levels at 40 \pm 10 ng/ml.

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Renal microvascular and tubular injuries in type II diabetic nephropathy

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To the Editor: We read Verzola *et al.*'s¹ article with great interest. The authors have pointed out the significance of glomerular cell injury and a correlation between the renal microvascular injury and the magnitude of tubulointerstitial fibrosis in type II diabetic nephropathy. Such correlation is further supported by recent intrarenal hemodynamic study, which reveals a phenomenon the so-called hemodynamic maladjustment secondary to glomerular endothelial cell

dysfunction, which is characterized by a preferential constriction of the efferent arteriole, and a subsequent reduction in peritubular capillary flow inducing a chronic ischemic injury to the tubulointerstitium.² The peritubular capillary flow reduction correlates inversely with the magnitude of tubulointerstitial fibrosis, and it progressively decreases as the disease severity increases from normoalbuminuric to albuminuric type II diabetic nephropathy. Thus, renal microvascular injury has a significant impact on renal disease progression. In this regard, it is mandatory to recognize renal microvascular disease at an early stage of type II diabetic nephropathy in which the mechanism of vascular repair is still adequately maintained,³ and treatment at this early stage under favourable environment is capable of restoring renal perfusion and function.⁴ To accomplish an effective preventive strategy of renal disease progression in type II diabetic nephropathy, it would require a more sensitive diagnostic marker than microalbuminuria, such as fractional excretion of magnesium, to screen early stage of diabetic nephropathy.⁵

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Response to 'Renal microvascular and tubular injuries in type II diabetic nephropathy'

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We thank Drs Narisa and Prasit Futrakul for their interest in our paper.¹ The findings observed in their studies, implying a maladaptive constriction of the efferent arteriole and downstream vascular and tubulointerstitial damage in type II diabetic patients, are appealing.² One of the basic abnormalities in diabetic nephropathy is microalbuminuria, which eventually progresses to proteinuria. Downstream into the tubular compartment, the

proteinuria induces a proinflammatory injury in tubular cells, which can ease the development of interstitial fibrosis and tubular atrophy.³ However, at variance with type I diabetic patients, a considerable number of type II diabetic patients, even with microalbuminuria or macroalbuminuria, have normal glomerular structure but show tubulointerstitial and/or arteriolar abnormalities.⁴ In type II diabetes, hyperglycemia⁵ and hypertension⁶ may cooperate to impair the physiologic mechanism that maintains normal glomerular capillary pressure and tubular function.^{6,7}

In our study, we evaluated apoptosis in renal biopsies obtained from patients with early or advanced type II diabetic nephropathy. We found that apoptotic changes are diffusely increased in glomeruli, tubuli, and vascular endothelia. According to our findings, apoptotic cell loss is already observed in proteinuric patients with normal or subnormal glomerular filtration rate and only modest biopsy changes, suggesting that the acceleration of apoptotic processes is an early phenomenon. Thus, besides being a pathogenic mechanism of cell loss, apoptosis can also be an additional tool for the evaluation of early kidney damage. In patients with more advanced disease, glomerular apoptosis is directly related to the histological scores of glomerular sclerosis, mesangial proliferation, and tubule atrophy.

Low serum magnesium level is an independent predictor of incident type II diabetes.⁸ In addition, hypomagnesemia has been linked to poor glycemic control and diabetes complication.⁹ We did not study kidney magnesium handling in our patients. However, the observation by Futrakul is interesting, as the increased incidence of hypomagnesemia among patients with type II diabetes has so far been considered multifactorial.⁹ We agree with their suggestions in studying the function of kidney tubule in patients with type II diabetes mellitus, as a clue for the occurrence of early microvascular damage. Further exploration of both the biology of renal cells and the mechanisms of diabetic disease will be critical for developing new preventive, diagnostic and therapeutic approaches to diabetic nephropathy.

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Rituximab in membranous nephropathy

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To the Editor: I sincerely congratulate Fervenza *et al.*¹ on their paper describing the effect of rituximab in idiopathic membranous nephropathy. In fact, I believe that their results might allow for a more optimistic assessment. Plotting from their Table 2, the proteinuria over the time from 6 months before treatment and until 12 months after treatment very clearly shows that nothing happens under the 6-month observation, but a clear course then develops afterward that does not end at 12 months. To show that, it is helpful to use a log-transformed proteinuria. Figure 1 indicates that the chosen method of analysis, a paired *t*-test based on the baseline to 12 months difference, is conservative and uses less information than is, in fact, available.

To analyze the figure, a linear mixed model,² with intercepts and slopes modeled ('random'), was made from the reported data using the freely available R.³ It was found that both time ($t = -3.45$, $P = 0.0008$) and creatinine

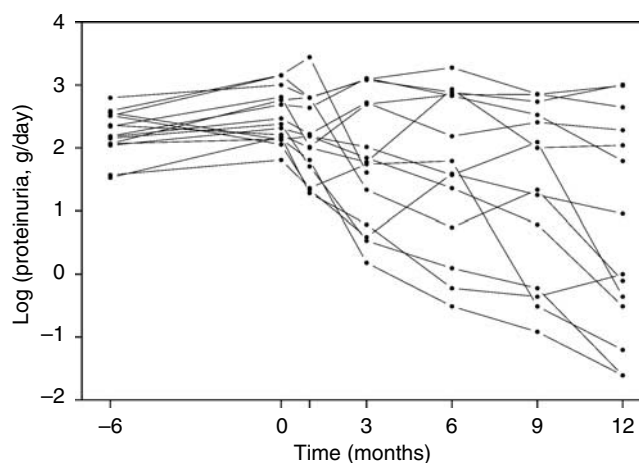


Figure 1 | Longitudinal effect of Rituximab on proteinuria (log transformed).